Identification and Functional Characterization of Rca1, a Transcription Factor Involved in both Antifungal Susceptibility and Host Response in Candida albicans

Titre	Identification and Functional Characterization of Rca1, a Transcription Factor Involved in both Antifungal Susceptibility and Host Response in Candida albicans
Type de publication	Article de revue
Auteur	Vandeputte, Patrick [1], Pradervand, Sylvain [2], Ischer, Françoise [3], Coste, Alix T. [4], Ferrari, Selene [5], Harshman, Keith [6], Sanglard, Dominique [7]
Editeur	American Society for Microbiology
Type	Article scientifique dans une revue à comité de lecture
Année	2012
Langue	Anglais
Date	2012/01/07
Numéro	7
Pagination	916 - 931
Volume	11
Titre de la revue	Eukaryotic Cell
ISSN	1535-9786
Résumé en anglais	The identification of novel transcription factors associated with antifungal response may allow the discovery of fungus-specific targets for new therapeutic strategies. A collection of 241 Candida albicans transcriptional regulator mutants was screened for altered susceptibility to fluconazole, caspofungin, amphotericin B, and 5-fluorocytosine. Thirteen of these mutants not yet identified in terms of their role in antifungal response were further investigated, and the function of one of them, a mutant of orf19.6102 (RCA1), was characterized by transcriptome analysis. Strand-specific RNA sequencing and phenotypic tests assigned Rca1 as the regulator of hyphal formation through the cyclic AMP/protein kinase A (cAMP/PKA) signaling pathway and the transcription factor Efg1, but also probably through its interaction with a transcriptional repressor, most likely Tup1. The mechanisms responsible for the high level of resistance to caspofungin and fluconazole observed resulting from RCA1 deletion were investigated. From our observations, we propose that caspofungin resistance was the consequence of the deregulation of cell wall gene expression and that fluconazole resistance was linked to the modulation of the cAMP/PKA signaling pathway activity. In conclusion, our large-scale screening of a C. albicans transcription factor mutant collection allowed the identification of new effectors of the response to antifungals. The functional characterization of Rca1 assigned this transcription factor and its downstream targets as promising candidates for the development of new therapeutic strategies, as Rca1 influences host sensing, hyphal development, and antifungal response.
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DOI	10.1128/EC.00134-12 [9]
Lien vers le document	http://dx.doi.org/10.1128/EC.00134-12 [9]

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